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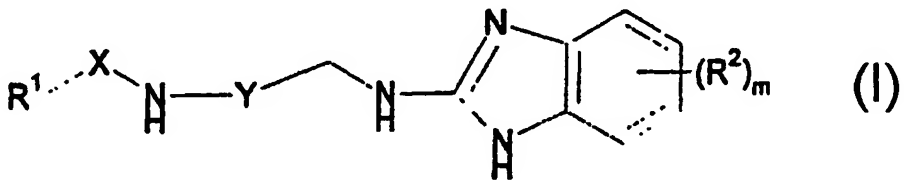

(I)

(57) Abstract: Compounds of formula (I) in which R^1 is an optionally substituted aryl or an optionally substituted heteroaryl ring; $(R^2)_m$ is hydrogen or selected substituents; X is CH_2 or CHR_3 in which R^3 is $C_{(1-6)}$ alkyl or is linked to the orthoposition of an aryl or heteroaryl ring of R^1 to form a 5 to 7 membered ring optionally including oxygen or nitrogen as a ring atom; Y is $C_{(1-3)}$ alkylene or $C_{(4-6)}$ cycloalkylene; are inhibitors of the bacterial enzyme *S aureus* methionyl t-RNA synthetase and are of use in treating bacterial infections.

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BENZIMIDAZOLE DERIVATIVES AND THEIR USE AS METHIONYL T-RNA SYNTHETASE INHIBITORS

The present invention relates to novel 2-NH-benzimidazoles which are inhibitors of methionyl t-RNA synthetase (MRS), processes for their preparation and their use in therapy as anti-bacterial agents.

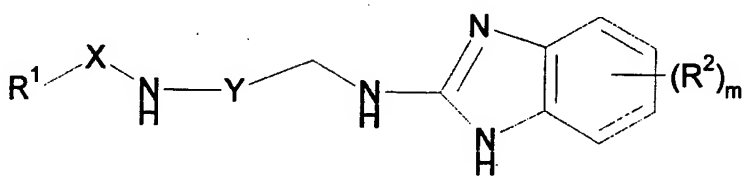
t-RNA synthetases are involved in protein biosynthesis so that inhibition thereof may be expected to lead to a cessation of cell growth. Thus, for instance, the compound mupirocin, produced by the organism *Pseudomonas fluorescens*, is an anti-bacterial agent and is used as the active ingredient in the product Bactroban, marketed by SmithKline Beecham. Mupirocin has been shown to be an inhibitor of the isoleucyl t-RNA synthetase. Each t-RNA synthetase represents a separate target for drug discovery. t-RNA synthetase inhibitors which are selective for bacterial cells over mammalian cells are of considerable therapeutic interest as they have the potential to be used as anti-bacterial agents.

The sequence of the t-RNA synthetase genes in organisms such as *S aureus* have recently been determined, see for instance European Patent application no 97300317.1 (SmithKline Beecham, *S aureus* MRS), thereby assisting the process of identifying inhibitors.

WO 99/ and WO 00/ (SmithKline Beecham, published after the priority date of the present application) describe a class of 2-(NH- or O- substituted) quinolones which are potent inhibitors of methionyl t-RNA synthetase

We have now found a further class of compounds which are potent inhibitors of methionyl t-RNA synthetase viz 2-NH - substituted benzimidazoles. The benzimidazole compound N-1H-benzimidazol-2-yl-N'-(phenylmethyl)-1,2-ethane diamine has been previously described but with no indication of any biological activity (Haerter et al, Helv Chim Acta, 854, 2114, 1971).

Accordingly, the present invention provides a compound of the formula (I):



(I)

in which:

R^1 is an optionally substituted aryl or an optionally substituted heteroaryl ring;

R^2 is selected from halo, cyano, hydroxy, $(C_1\text{-}6)$alkyl (optionally substituted by halo, hydroxy, amino, mono to perfluoro$(C_1\text{-}3)$alkyl, carboxy or $(C_1\text{-}6)$alkoxycarbonyl), $(C_3\text{-}7)$cycloalkyl, $C_{(1\text{-}6)}$alkoxy, amino, mono- or di-$(C_1\text{-}6)$alkylamino, acylamino, carboxy, $(C_1\text{-}6)$alkoxycarbonyl, carboxy$(C_1\text{-}6)$alkyloxy, $(C_1\text{-}6)$alkylthio, $(C_1\text{-}6)$alkylsulphinyl, $(C_1\text{-}6)$alkylsulphonyl, sulphamoyl, mono- and di-$(C_1\text{-}6)$alkylsulphamoyl, carbamoyl, mono- and di-$(C_1\text{-}6)$alkylcarbamoyl, and heterocyclyl;

m is 0 or an integer from 1 to 3;

X is CH_2 or CHR^3 in which R^3 is $C_{(1\text{-}6)}$alkyl or is linked to the ortho position of an aryl or heteroaryl ring of R^1 to form a 5 to 7 membered ring optionally including oxygen or nitrogen as a ring atom;

Y is $C_{(1\text{-}3)}$alkylene or $C_{(4\text{-}6)}$cycloalkylene;

including tautomeric forms of the imidazole ring; and

salts thereof, preferably pharmaceutically acceptable salts thereof; and excluding *N*-1H-benzimidazol-2-yl-*N'*-(phenylmethyl)-1,2-ethane diamine.

Compounds of formula (I) are inhibitors of *S aureus* methionyl t-RNA synthetase.

Representative examples of R^1 when aryl include phenyl and naphthyl, each of which may be optionally substituted with up to four substituents. Representative examples of such substituents include $C_{(1\text{-}6)}$ alkyl, $C_{(1\text{-}6)}$ alkoxy, include alkylthio, halo, cyano, amino, sulphamoyl, phenylcarbonyl, aryl, and benzyloxy. Preferably, the phenyl or naphthyl is substituted by two or three lipophilic substituents such as chloro, bromo, iodo, methyl, methoxy, ethoxy, allyloxy, phenethyloxy or trifluoromethyl.

Representative examples of R^1 when heteroaryl include pyrrolyl, thienyl, furanyl, pyridyl, quinolinyl, benzofuranyl, and indolyl, each of which may be optionally substituted with up to three substituents. Preferably, the heteroaryl ring is substituted by two or three lipophilic substituents such as chloro, bromo, iodo, methyl, methoxy or trifluoromethyl. Representative examples of such substituents include halo.

Preferred examples of aryl and heteroaryl groups for R^1 include phenyl, indolyl and thienyl.

Representative examples of X include CH_2 or forming with R^1 a 5-7-membered ring fused to an aryl or heteroaryl ring, preferably including oxygen or nitrogen as a ring atom, for instance chroman-4-yl and 1,2,3,4-tetrahydroquinolin-4-yl in which R^1 is phenyl

Representative examples of R^1X include benzyl, chroman-4-yl, 1,2,3,4-tetrahydroquinolin-4-yl, indol-2-ylmethyl, and thien-2-ylmethyl in which the aryl/heteroaryl ring may be optionally substituted as hereinbefore defined. Preferably, R^1X is optionally substituted benzyl, 1,2,3,4-tetrahydroquinolin-4-yl or indol-2-ylmethyl.

Representative examples of Y include a C_2 alkylene chain or a 1,2-cyclopentylene group. Preferably, Y is a C_2 alkylene chain.

Salts may be formed from inorganic and organic acids. Representative examples of suitable inorganic and organic acids from which pharmaceutically acceptable salts of compounds of formula (I) may be formed include maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

When used herein, the term "alkyl" and similar terms such as "alkoxy" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

Preferred substituents for an alkyl group include, for example, and unless otherwise defined, halogen, cyano, azido, nitro, carboxy, (C_{1-6})alkoxycarbonyl, carbamoyl, mono- or di-(C_{1-6})alkylcarbamoyl, sulpho, sulphamoyl, mono- or di-(C_{1-6})alkylsulphamoyl, amino, mono- or di-(C_{1-6})alkylamino, acylamino, ureido, (C_{1-6})alkoxycarbonylamino, 2,2,2-trichloroethoxycarbonylamino, aryl, heterocyclyl, hydroxy, (C_{1-6})alkoxy, acyloxy, oxo, acyl, 2-thienoyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, hydroxyimino, (C_{1-6})alkoxyimino, hydrazino, hydrazono, benzohydroximoyl, guanidino, amidino and iminoalkylamino.

When used herein, the term "aryl" includes, unless otherwise defined, phenyl or naphthyl optionally substituted with up to five, preferably up to three substituents.

When substituted, an aryl group may have up to three substituents. Preferred substituents for an aryl group include, for example, and unless otherwise defined, halogen, cyano, (C_1-$_6$)alkyl, mono to perfluoro(C_1-$_3$)alkyl, (C_3-$_7$)cycloalkyl, (C_2-$_6$)alkenyl, (C_1-$_6$)alkoxy, (C_2-$_6$)alkenoxy, aryl$C_{(1-6)}$alkoxy, halo(C_1-$_6$)alkyl, hydroxy, amino, mono- or di-(C_1-$_6$)alkylamino, acylamino, nitro, carboxy, (C_1-$_6$)alkoxycarbonyl, (C_1-$_6$)alkenyloxycarbonyl, (C_1-$_6$)alkoxycarbonyl(C_1-$_6$)alkyl, carboxy(C_1-$_6$)alkyl, (C_1-$_6$)alkylcarbonyloxy, carboxy(C_1-$_6$)alkyloxy, (C_1-$_6$)alkoxycarbonyl(C_1-$_6$)alkoxy, (C_1-$_6$)alkylthio, (C_1-$_6$)alkylsulphinyl, (C_1-$_6$)alkylsulphonyl, sulphamoyl, mono- and di-(C_1-$_6$)-alkylsulphamoyl, carbamoyl, mono- and di-(C_1-$_6$)alkylcarbamoyl, and heterocyclyl.

When used herein, the term "heteroaryl" includes single or fused rings comprising up to four hetero-atoms in the ring selected from oxygen, nitrogen and sulphur and optionally substituted with up to three substituents. Preferably the heteroaryl ring comprises from 4 to 7, preferably 5 to 6, ring atoms. A fused heteroaryl ring system may include carbocyclic rings and need only include one heterocyclic ring.

When used herein, the term "heterocyclyl" includes aromatic and non-aromatic single or fused rings comprising up to four hetero-atoms in the ring selected from oxygen, nitrogen and sulphur and optionally substituted with up to three substituents. Suitably the heterocyclic ring comprises from 4 to 7, preferably 5 to 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need only include one heterocyclic ring.

When substituted, a heteroaryl or a heterocyclyl group may have up to three substituents. Preferred such substituents include those previously mentioned for an aryl group as well as oxo.

When used herein, the terms 'halogen' and 'halo' include fluorine, chlorine, bromine and iodine and fluoro, chloro, bromo and iodo, respectively.

The compounds according to the invention are suitably provided in substantially pure form, for example at least 50% pure, suitably at least 60% pure, advantageously at least 75% pure, preferably at least 85% pure, more preferably at least 95% pure, especially at least 98% pure, all percentages being calculated as weight/weight. An impure or less pure form of a compound according to the invention may, for example, be used in the preparation of a more pure form of the

same compound or of a related compound (for example a corresponding derivative) suitable for pharmaceutical use.

Preferred compounds of formula (I) include:

2-[3-(6,8-Dibromo-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]-1*H*-benzimidazole;

2-[3-(4,6-Dichloroindol-2-ylmethylamino)prop-1-ylamino]-1*H*-benzimidazole;

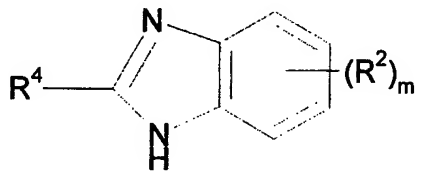
2-[3-(6-Ethyl-8-iodo-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]-1*H*-benzimidazole;

2-{3-[4,6-Dichloro-1-(2-hydroxyethyl)-1*H*-indol-2-ylmethylamino]prop-1-ylamino}-1*H*-benzimidazole;

2-[3-(2-Ethoxy-5-iodo-3-methylbenzylamino)prop-1-ylamino]-1*H*-benzimidazole; and

2-[3-(4-Trifluoromethyl-6-methoxyindol-2-ylmethylamino)prop-1-ylamino]-1*H*-benzimidazole.

A compound of formula (I) may be prepared by reacting an imidazole compound of formula (II):



(II)

in which R^2 and m are as hereinbefore defined; and

R^4 is a leaving group such as halo, for instance chloro, or $C_{(1-6)}$ alkylthio;

with an amine of the formula (III):

$$R^1XNHYCH_2NH_2$$

(III)

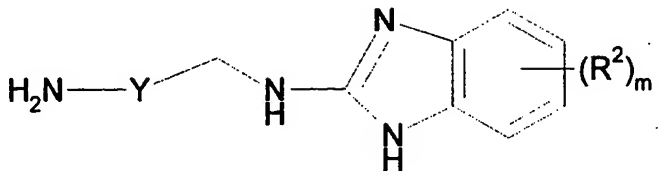
in which R^1, X and Y are as hereinbefore defined;

or an activated derivative thereof;

under nucleophilic displacement conditions.

Suitable conditions are well known in the art and include the use of a large excess of the compound of formula (III) to drive the reaction to completion and heating at a temperature of 60 - 130 °C. Addition of a base may be advantageous in some cases, eg a tertiary base such as *N,N*-di(cyclohexyl)ethylamine.

A compound of formula (I) may also be prepared by reacting a compound of formula (IV):



(IV)

in which m, R^2 and Y are as hereinbefore defined;
with either:

(a) for a compound of formula (I) in which X is CH_2, an aldehyde of formula (V):

$$R^1CHO \qquad (V)$$

in which R^1 is as hereinbefore defined;
under reductive alkylation conditions;

(b) for a compound of formula (I) in which X is CH_2 substituted by $C_{(1-6)}$ alkyl or in which R^1 and X are linked by a 5-7-membered ring opt.cont. oxygen or nitrogen,, a ketone of formula (VI):

$$R^1R^3CO \qquad (VI)$$

in which R^1 and R^3 are as hereinbefore defined;
under reductive alkylation conditions.

Suitable reductive alkylating conditions are well known in the art and include for instance, the use of sodium triacetoxyborohydride in a solvent system such as DMF/acetic acid or sodium cyanoborohydride in methanol/acetic acid. Reductive alkylation with an aldehyde is typically carried out at room temperature for a period of 1 - 16 h. Reductive alkylation with a ketone is typically carried out in refluxing methanol for a period of 16 - 40 h.

A compound of formula (IV) may be prepared by reacting a compound of formula (II) with a compound of formula (III) in which R^1X is hydrogen.

The compounds of this invention are active against both Gram negative and Gram positive organisms, including *Haemophilus*, for instance *H. influenzae*

Q1; *Moraxella*, for instance *M. catarrhalis* 1502; *Streptococci*, for instance *S. pyogenes* CN10 and *S. pneumoniae* R6; *Staphylococci*, for instance *S. aureus* Oxford; *Escherichia*, for instance *E. Coli* DC0, and *Enterococci*, for instance *Ent. faecelis* I. In addition, compounds of this invention are active against *Staphylococci* organisms such as *S. aureus* and coagulase-negative strains of *Staphylocci* such as *S. epidermidis* which are resistant (including multiply-resistant) to other anti-bacterial agents, for instance, β-lactam antibiotics such as, for example, methicillin; macrolides; aminoglycosides, and lincosamides. Compounds of the present invention are therefore useful in the treatment of MRSA, MRCNS and MRSE. Compounds of the present invention are also active against strains of *E. faecalis* including vancomycin resistant strains and therefore of use in treating infections associated with VRE organisms. Furthermore, compounds of the present invention are useful in the treatment of *Staphylococci* organisms which are resistant to mupirocin.

Bacterial infections which may be treated include respiratory tract infections, otitis media, meningitis, endocarditis, skin and soft tissue infections in man, mastitis in cattle, and respiratory infections in animals such as pigs and cattle. Accordingly, in a further aspect, the present invention provides a method of treating bacterial infection in human or non-human animals, which method comprises administering a therapeutically effective amount of a compound of formula (I) as hereinbefore defined, to a human or non-human animal in need of such therapy.

The present invention provides a pharmaceutical composition comprising a compound of formula (I) together with a pharmaceutically acceptable carrier or excipient.

The present invention also provides a method of treating bacterial infections in animals, especially in humans and in domesticated mammals, which comprises administering a compound of formula (I), or a composition according to the invention, to a patient in need thereof.

The invention further provides the use of a compound of formula (I) in the preparation of a medicament composition for use in the treatment of bacterial infections.

The compounds and compositions according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

The compounds and compositions according to the invention may be formulated for administration by any route, for example oral, topical or parenteral. The compositions may, for example, be made up in the form of tablets, capsules, powders, granules, lozenges, creams, syrups, or liquid preparations, for example solutions or suspensions, which may be formulated for oral use or in sterile form for parenteral administration by injection or infusion.

Tablets and capsules for oral administration may be in unit dosage form, and may contain conventional excipients including, for example, binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; and pharmaceutically acceptable wetting agents, for example sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or another suitable vehicle before use. Such liquid preparations may contain conventional additives, including, for example, suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters (for example glycerine), propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and, if desired, conventional flavouring and colour agents.

Compositions according to the invention intended for topical administration may, for example, be in the form of ointments, creams, lotions, eye ointments, eye drops, ear drops, impregnated dressings, and aerosols, and may contain appropriate conventional additives, including, for example, preservatives, solvents to assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, and ethanol or oleyl alcohol for lotions. Such carriers may constitute from about 1% to about 98% by weight of the formulation; more usually they will constitute up to about 80% by weight of the formulation.

Compositions according to the invention may be formulated as suppositories, which may contain conventional suppository bases, for example cocoa-butter or other glycerides.

Compositions according to the invention intended for parenteral administration may conveniently be in fluid unit dosage forms, which may be prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, may be either suspended or dissolved in the vehicle. In preparing solutions, the compound may be dissolved in water for injection and filter-sterilised before being filled into a suitable vial or ampoule, which is then sealed. Advantageously, conventional additives including, for example, local anaesthetics, preservatives, and buffering agents can be dissolved in the vehicle. In order to enhance the stability of the solution, the composition may be frozen after being filled into the vial, and the water removed under vacuum; the resulting dry lyophilized powder may then be sealed in the vial and a accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions may be prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The compound may instead be sterilised by exposure to ethylene oxide before being suspended in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in such suspensions in order to facilitate uniform distribution of the compound.

A compound or composition according to the invention may suitably be administered to the patient in an antibacterially effective amount.

A composition according to the invention may suitably contain from 0.1% by weight, preferably from 10 to 60% by weight, of a compound according to the invention (based on the total weight of the composition), depending on the method of administration.

The compounds according to the invention may suitably be administered to the patient at a daily dosage of from 1.0 to 50 mg/kg of body weight. For an adult human (of approximately 70 kg body weight), from 50 to 3000 mg, for example about 1500 mg, of a compound according to the invention may be administered daily. Suitably, the dosage for adult humans is from 5 to 20 mg/kg per day. Higher or lower dosages may, however, be used in accordance with normal clinical practice.

When the compositions according to the invention are presented in unit dosage form, each unit dose may suitably comprise from 25 to 1000 mg, preferable from 50 to 500 mg, of a compound according to the invention.

The following Examples illustrate the present invention.

General method for alkylation of phenols To a solution of the phenol (1.2 mmol) and ethyl iodide (480 ul, 6 mmol) in dimethylformamide (2 ml) was added potassium carbonate (330 mg, 2.4 mmol). After stirring under argon at 65°C for 16 h the suspension was then diluted with diethyl ether, washed with water, dried ($MgSO_4$) and evaporated to afford the product.

General method for reductive amination To a suspension of the amine (0.2 mmol) (containing 0.5 mmol sodium acetate if the amine was present as the dihydrochloride) in methanol (2 ml) was added the aldehyde (0.2 mmol) in methanol (2 ml) and acetic acid (0.033 ml) . After stirring under argon for 10 min, $NaCNBH_3$ (24 mg, 0.4 mmol) in MeOH (1 ml) was added and the reaction stirred for 16 h. The reaction mixture was applied to a 2 g Varian Bond Elute SCX cartridge which was flushed with MeOH (8 ml). The cartridge was then eluted with 8 ml 0.2 M NH_3 in MeOH, and this eluate evaporated to dryness. The residue was purified by chromatography on silica gel eluting with 2-10% (9:1 MeOH/20 M NH_3) in CH_2Cl_2 . Product-containing fractions were combined and evaporated under reduced pressure to give the product as a white solid. To convert this into the corresponding dihydrochloride, the solid was dissolved in 1.0 M HCl in methanol (0.4 ml) and the solution evaporated to dryness. When polymer-supported $CNBH_3$ (Novabiochem) was used, work-up consisted of filtration and evaporation, followed by chromatography on silica gel as described above.

Example 1 - 2-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-1*H*-benzimidazole

a) *N*-(3,5-Dibromobenzyl)propane-1,3-diamine: 3,5-Dibromobenzyl bromide (9.96 g, 30.2 mmol) was dissolved in THF (70 ml) and added dropwise over 90 minutes to a solution of propane-1,3-diamine (12.6 ml, 151 mmol) in THF (50 ml) at 60°C. The solution was stirred under argon for a further 30 min, filtered and the filtrate concentrated. The residues were partitioned between *tert*-butylmethylether and H_2O, the organic layer separated and aqueous HCl (1 M) added. The aqueous layer was separated, filtered and basified to pH 13 (NaOH pellets). The solution was extracted with $CHCl_3$, dried (K_2CO_3), and evaporated under reduced pressure to yield the **title compound** as a yellow oil (6.21 g, 19 mmol): δ_H ($CDCl_3$) 1.36 (br, s, 3H + H_2O), 1.65 (m, 2H), 2.67 (t, *J* 6.7, 2H), 2.79 (t, *J* 6.7, 2H), 3.74 (s, 2H), 7.42 (d, *J* 1.6, 2H), 7.54 (t, *J* 1.6, 1H,); MS (ES+) 323 (100%, $[M+H]^+$), 306 (75), 249 (100).

b) 2-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-1*H*-benzimidazole: 2-Chloro-1*H*-benzimidazole (0.018 g, 0.12 mmol) was treated under argon with *N*-(3,5-dibromobenzyl)propane-1,3-diamine, **Example 1a,** (0.076 g, 0.24 mmol) at

135°C for 3 h. The crude product was chromatographed on silica gel eluting with an increasing concentration of 9:1 methanol/ammonia in dichloromethane to give the **title compound**, as a colourless gum (0.01g, 19%). δ_H (CD_3OD) 1.95 (2H, m), 2.8 (2H, t, J=7.1Hz), 3.5 (2H, t, J=6.8Hz), 3.8 (2H, s), 7.05 (2H, m), 7.25 (2H, m), 7.6 (2H, d, J=1.6Hz), 7.7 (1H, t, 1.6Hz). MS (ES^+) 437, 439, 441 (6, 13, 7%) MH^+.

Example 2 - 2-[3-(2-Ethoxy-3,5-dibromobenzylamino)prop-1-ylamino]-1*H*-benzimidazole

a) 2-(3-Aminopropylamino)benzimidazole

2-Chloro-1*H*-benzimidazole (1.53 g, 10 mmol) and 1,3-diaminopropane (25 ml, 300 mmol) were heated together for 18 h at 90°C, then at 120°C for 72 h. The solution was evaporated to dryness, then triturated with dichloromethane to afford a pale brown powder. This powder was dissolved in methanol and pre-absorbed onto silica. Flash chromatography, eluting with 9-20% '10% 0.880 ammonia in methanol' in dichloromethane, gave the title compound as a buff powder (1.45 g, 76%); δ_H (CD_3OD) 1.73 (2H, quintet), 2.69 (2H, t), 3.34 (2H, t), 6.82 – 6.92 (2H, m), and 7.04 – 7.13 (2H, m); LC/MS (ES+) 191 (100%, MH^+).

b) 2-[3-(2-Ethoxy-3,5-dibromobenzylamino)prop-1-ylamino]-1*H*-benzimidazole: 2-(3-Aminopropylamino)-1*H*-benzimidazole, **Example 2a,** (0.029 g, 0.15 mmol) was dissolved in methanol (1.5 ml) and acetic acid (0.1 ml). To this was added 3,5-dibromo-2-ethoxybenzaldehyde (0.046 g, 0.15 mmol) followed by sodium cyanoborohydride (0.019 g, 0.3 mmol). The mixture was stirred at room temperature. After 16 h it was purified on a SCX cartridge, washing first with methanol, then eluting the product with 0.1M ammonia in methanol. This gave the **title compound** as a white powder (0.055 g, 76%); δ_H (CD_3OD) 1.38 (3H, t), 1.87 (2H, quintet), 2.72 (2H, t), 3.44 (2H, t), 3.81(2H, s), 3.97 (2H, q), 6.91 – 7.01 (2H, m), 7.11 – 7.21 (2H, m), 7.57 (1H, d), and 7.65 (1H, d); LC/MS (ES+) 481, 483, 485 (50, 100, 50%, MH^+).

Example 3 - 2-[3-(6,8-Dichlorochroman-4-ylamino)prop-1-ylamino]-1*H*-benzimidazole : 2-(3-Aminopropylamino)-1*H*-benzimidazole, **Example 2a,** (0.029 g, 0.15 mmol) was dissolved in methanol (2 ml) and acetic acid (0.1 ml). To this was added 6,8-dichlorochroman-4-one (0.054 g, 0.25 mmol), followed by sodium cyanoborohydride (0.025 g, 0.4 mmol). The mixture was refluxed for 26 h. After cooling, it was purified on a SCX cartridge, washing first with methanol, then eluting the product with 0.1M ammonia in methanol. This gave the **title compound** as a white solid (0.042 g, 72%); δ_H (CD_3OD) 1.86 – 1.95 (2H, m), 2.02 – 2.09 (2H, m), 2.76 – 2.88 (2H, m), 3.48 (2H, t), 3.83(1H, t), 4.26 – 4.44

(2H, m), 6.94 – 7.00 (2H, m), 7.15 – 7.21 (2H, m), 7.27 (1H, d), and 7.33 (1H, d); LC/MS (ES+) 391,393 (100, 67%, MH^+).

Example 4 - 2-[3-(6,8-Dibromo-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]-1*H*-benzimidazole : The **title compound** was prepared in a similar way to **Example 3**, to give a white foam (0.044 g, 61%); δ_H (CD_3OD) 1.77 – 2.09 (4H, m), 2.74 – 2.85 (2H, m), 3.30 – 3.49 (4H, m), 3.72(1H, t), 6.93 – 7.00 (2H, m), 7.13 – 7.21 (2H, m), 7.24 (1H, d), and 7.38 (1H, d); LC/MS (ES+) 478, 480, 482 (50, 100, 50%, MH^+).

Example 5 - 2-[3-(4,6-Dichloroindol-2-ylmethylamino)prop-1-ylamino]-1*H*-benzimidazole

a) Sodium tris-(diethylamino)aluminium hydride: To sodium aluminium hydride (1M in THF, 2 ml) in THF (2 ml) cooled to 0°C under argon was added dropwise diethylamine (0.62 ml, 6 mmol). The solution was stirred at 0°C for 75 min to give a final volume of 2.4 ml.

b) 4,6-Dichloroindole-2-carboxaldehyde: To ethyl 4,6-dichloroindole-2-carboxylate (0.24 g, 0.96 mmol) in THF (2 ml) cooled to 0°C under argon was added dropwise 1.2 ml of the solution of sodium tris-(diethylamino)aluminium hydride prepared in **Example 5a**. After 1 h at 0°C the reaction was quenched by the addition of 5% aqueous citric acid (20 ml)and the mixture extracted with diethyl ether (2 x 20 ml). The organic layer was dried and evaporated to a yellow solid, 0.25 g. NMR revealed the presence of approx 40% of the title aldehyde δ_H ($CDCl_3$) 9.9.

c) 2-[3-(4,6-Dichloroindol-2-ylmethylamino)prop-1-ylamino]-1*H*-benzimidazole: To 2-(3-aminopropylamino)-1*H*-benzimidazole, **Example 2a,** (0.038 g, 0.2 mmol) was added the crude product from **Example 5b**. (0.125 g) in methanol (3 ml), acetic acid (0.024 g) and sodium cyanoborohydride (0.016 g, 0.25 mmol). After 1.5 h the reaction mixture was applied to a 1 g SCX cartridge which was flushed with MeOH (20 ml). The cartridge was then eluted with 10 ml 0.2M NH_3 in MeOH, and this eluate evaporated to dryness. Further purification by chromatography over silica gel eluting with an increasing concentration of 9:1 methanol/ammonia in dichloromethane gave the **title compound**, isolated as a colourless foam (0.024 g, 31%). δ_H (Methanol-D_4) 1.95 (2H, m), 2.8 (2H, t, J=7.1Hz), 3.5 (2H, t, J=6.8Hz), 4.0 (2H, s), 6.5 (1H, m), 7.05 (2H, m), 7.1 (1H, d, J=1.6Hz), 7.2 (2H, m), 7.3 (1H, t, 1.6Hz). MS (ES^+) 388, 390 (30, 20%) MH^+.

Example 6 - 2-[3-(6-Ethyl-8-iodo-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]-1*H*-benzimidazole dihydrochloride

6-Ethyl-8-iodo-2,3-dihydro-1*H*-quinolin-4-one **(ref. P32159)** (60 mg) and **example 2a** (38 mg) were dissolved in 3% v/v acetic acid in methanol (5 ml). Sodium cyanoborohydride (50 mg in total) was added and the reaction mixture heated to 85°C for a total of 76 h. The reaction mixture was passed down a cation exchange cartridge and the residue purified by column chromatography. The product was converted to the corresponding dihydrochloride salt using conc. HCl in methanol to yield the **title compound** as an off-white solid: (27 mg, 25%), *m/z* (ESI) 476 ($M+H^+$, 10%), 286 (100%).

Example 7 - 2-[3-(4,5-Dibromothien-2-yl)methylamino)prop-1-ylamino]-1*H*-benzimidazole dihydrochloride

Example 2a (0.029 g, 0.15 mmol) was dissolved in methanol (1.5 ml) and acetic acid (0.1 ml). To this was added 4,5-dibromothiophene-2-carbaldehyde (0.041 g, 0.15 mmol) followed by sodium cyanoborohydride (0.019 g, 0.3 mmol). The mixture was stirred at room temperature. After 3 h it was purified on a SCX cartridge, washing first with methanol, then eluting the product with 0.1M ammonia in methanol. The product was further purified by flash chromatography, eluting with with 0 – 10% '10% 0.880 ammonia in methanol' in dichloromethane, to give the free base. This was suspended in methanol, treated with hydrochloric acid and then evaporated to dryness. The resultant solid was triturated with diethyl ether to give the **title compound** as a white powder (0.047 g, 61%); LC/MS (ES+) 443, 445, 447 (50, 100, 50%, MH^+).

Example 8 - 2-{3-[4,6-Dichloro-1-(2-hydroxyethyl)-1*H*-indol-2-ylmethylamino]prop-1-ylamino}-1*H*-benzimidazole

a) 4,6-Dichloro-1-(methoxycarbonylmethyl)-1*H*-indole-2-carboxylic acid ethyl ester 4,6-Dichloro-1*H*-indole-2-carboxylic acid ethyl ester (0.516 g, 2 mmol) was disolved in DMF (5 ml) and then potassium carbonate (0.276 g, 2 mmol) was added. The mixture was stirred under argon for 30 min, then methyl bromoacetate (0.19 ml, 2 mmol) added. The mixture was stirred for a further 2.5 h, then diluted with water and extracted with diethyl ether. The combined organic extracts were washed with brine, dried and evaporated to give the **title compound** as a beige powder (0.65 g, 98%); MS (APCI +ve) 330, 332 (30, 21%, MH^+).

b) 2-(4,6-Dichloro-2-hydroxymethyl-1*H*-indol-1-yl)ethanol 4,6-Dichloro-1-(methoxycarbonylmethyl)-1*H*-indole-2-carboxylic acid ethyl ester (0.625 g, 1.89 mmol) was dissolved in THF (20 ml), cooled in an ice/salt bath under argon, and treated slowly with a solution of lithium aluminium hydride (1M in THF, 2.27 ml, 2.27 mmol). The mixture was stirred for 2 h then quenched carefully with water and extracted with ethyl acetate. The combined organic extracts were washed with

brine, dried and evaporated to give the crude product as an oily solid (0.5 g, q). This material was used without further purification.

c) 4,6-Dichloro-1-(2-hydroxyethyl)-1*H*-indole-2-carbaldehyde The crude material (max 1.89 mmol) from **b)** above was dissolved in dichloromethane (50 ml), manganese dioxide (1.64 g, 18.9 mmol) was added, and the mixture stirred for 3.5 h. The mixture was filtered, washing well with dichloromethane and 1,4-dioxane, then evaporated to give a solid. This material was dissolved in dichloromethane, pre-absorbed onto silica, then purified by flash chromatography, eluting with 0 – 20% ethyl acetate in 40 – 60 pet ether, to give the **title compound** as a white powder (0.203 g, 39%); MS (APCI –ve) 257, 259 (100, 66%, $M-H^-$).

d) 2-{3-[4,6-Dichloro-1-(2-hydroxyethyl)-1*H*-indol-2-ylmethylamino]prop-1-ylamino}-1*H*-benzimidazole. Example 2a (0.038 g, 0.2 mmol) was dissolved in methanol (1.5 ml) and acetic acid (0.1 ml). To this was added 4,6-dichloro-1-(2-hydroxyethyl)-1*H*-indole-2-carbaldehyde (0.052 g, 0.2 mmol) in methanol (0.5 ml). After 0.5 h sodium cyanoborohydride (0.025 g, 0.4 mmol) in methanol (0.5 ml) was added. The mixture was stirred at room temperature for 18 h then passed through a SAX cartridge, eluting with methanol. After evaporation, the crude product was further purified by flash chromatography, eluting with 0 – 10% '10% 0.880 ammonia in methanol' in dichloromethane, to give the **title compound** as a white powder (0.065 g, 76%); LC/MS (ES+) 432, 434 (15, 10%, MH^+).

Example 9 - 2-[3-(2-Ethoxy-3,5-dichlorobenzylamino)prop-1-ylamino]-1*H*-benzimidazole

a) 3,5-Dichloro-2-ethoxybenzaldehyde 3,5-Dichloro-2-hydroxybenzaldehyde was alkylated on a 5.2 mmol scale using the **general method for alkylation of phenols** to give the **title compound** as a yellow solid (1.14 g, 99%); *m/z* (ES^+) 219 (MH^+, 70%).

b) 2-[3-(2-Ethoxy-3,5-dichlorobenzylamino)prop-1-ylamino]-1*H*-benzimidazole 3,5-Dichloro-2-ethoxybenzaldehyde was coupled to **example 2a** on a 0.2 mmol scale using the **general method for reductive amination** to give the **title compound** as a white solid (30 mg, 32%); *m/z* (ES^+) 393 (MH^+, 40%).

Example 10 - 2-[3-(3-Bromo-2-ethoxy-5-methoxybenzylamino)prop-1-ylamino]-1*H*-benzimidazole

a) 3-Bromo-2-hydroxy-5-methoxybenzaldehyde 2-Hydroxy-5-methoxybenzaldehyde (3.0 g, 19.7 mmol) was dissolved in acetic acid (15 ml), treated with sodium acetate (1.8 g, 21.9 mmol) and cooled to 5 C. A solution of bromine (3.0 g, 18.7 mmol) in acetic acid (6 ml) was added dropwise. After stirring at room temperature for 4 h, the suspension was treated with water and the

yellow solid filtrated and dried to give the **title compound** (3.58 g, 79%); *m/z* (ES^-) 229 ($[M-H]^-$, 15%).

b) 3-Bromo-2-ethoxy-5-methoxybenzaldehyde 3-Bromo-2-hydroxy-5-methoxybenzaldehyde was alkylated on a 4.6 mmol scale using the **general method for alkylation of phenols** to give, after chromatography on Kieselgel 60 eluting with 50-80% dichloromethane in hexane, the **title compound** as a white solid (540 mg, 46%); *m/z* (ES^+) 259 (MH^+, 100%).

c) 2-[3-(3-Bromo-2-ethoxy-5-methoxybenzylamino)prop-1-ylamino]-1*H*-benzimidazole The product from **2b** was coupled to **example 2a** on a 0.2 mmol scale using the **general method for reductive amination** to give the **title compound** as a white solid (59 mg, 69%); *m/z* (ES^+) 433 (MH^+, 100%).

Example 11 - 2-[3-(2-Ethoxy-5-iodo-3-methylbenzylamino)prop-1-ylamino]-1*H*-benzimidazole

a) 2-Hydroxy-5-iodo-3-methylbenzaldehyde 2-Hydroxy-3-methylbenzaldehyde (272 mg, 2.0 mmol) was dissolved in dimethylformamide (10 ml), treated with sodium iodide (360 mg, 2.4 mmol) then chloramine T (546 mg, 2.4 mmol). After stirring at room temperature for 4 h, the suspension was treated with water, acidified with 1N HCl and the mixture extracted with ethyl acetate. The organic layer was washed successively with a 5% aqueous solution of sodium thiosulphate, brine then dried and evaporated. The residue was chromatographed on Kieselgel 60 eluting with 0-50% toluene in hexane. Product-containing fractions were combined and evaporated to give the **title compound** as a white solid (330 mg, 63%); *m/z* (AP^-) 261 ($[M-H]^-$, 20%).

b) 2-Ethoxy-5-iodo-3-methybenzaldehyde 2-Hydroxy-5-iodo-3-methylbenzaldehyde was alkylated on a 1.2 mmol scale using the **general method for alkylation of phenols** to give the **title compound** as a white solid (350 mg, 100%); δ_H ($CDCl_3$) 1.43 (3H, t, J =7.0 Hz, CH_3), 2.29 (3H, s, CH_3), 3.99 (2H, q, J =7.0 Hz, OCH_2), 7.74 (1H, d, J =2.3 Hz, Ar-H), 7.96 (1H, d, J=2.3 Hz, Ar-H), 10.25 (1H, s, CHO).

c) 2-[3-(2-Ethoxy-5-iodo-3-methylbenzylamino)prop-1-ylamino]-1*H*-benzimidazole 2-Ethoxy-5-iodo-3-methybenzaldehyde was coupled to **example 2a** on a 0.2 mmol scale using the **general method for reductive amination** to give the **title compound** as a white solid (71 mg, 75%); *m/z* (ES^+) 465 (MH^+, 100%).

Example 12 - 2-[3-(4-Trifluoromethyl-6-methoxyindol-2-ylmethylamino)prop-1-ylamino]-1*H*-benzimidazole

a) 3-Methoxy-5-trifluoromethylphenylhydrazine 3-Methoxy-5-trifluoromethylaniline (1.91 g, 10 mmol), in acetic acid (8 ml), conc. HCl (2.5 ml)

and methanol (4 ml) was cooled to 0°C and sodium nitrite (690 mg, 10 mmol) in water (2 ml) was added. The resulting bright orange mixture was added to stannous chloride (4.2 g, 22 mmol) in conc. HCl (9 ml) under argon. After 1.5 h water (30 ml) was added and the mixture extracted with dichloromethane. The aqueous layer was basified with solid potassium hydroxide. Diethyl ether (50 ml) was added and the mixture filtered through celite. The layers were separated and the aqueous layer extracted with more diethyl ether. The combined organic layers were washed with brine and dried ($MgSO_4$) to give the **title compound** as a white solid, (1.8 g, 87%).

b) Ethyl pyruvate 3-methoxy-5-trifluoromethylphenyl-E-hydrazone To the product from **a)** (0.9 g, 4.37 mmol) in ethanol (5 ml) was added ethyl pyruvate (0.547 ml, 5 mmol) and acetic acid (0.1 ml). The mixture was heated to reflux for 15min then cooled and evaporated to low volume under reduced pressure. Toluene (50 ml) was added and evaporated under reduced pressure and the residue triturated with hexane to give the **title compound** as a white solid (1.12 g, 84%).

c) Ethyl 4-trifluoromethyl-6-methoxyindole-2-carboxylate The hydrazone from **b)** (1.094 g, 4.3 mmol) and polyphosphoric acid (9 g) were heated to 75°C for 40 min. The mixture was cooled and triturated with ice water to give approximately 1 g of a white solid. This was purified by chromatography on silica gel eluting with 40-100% dichloromethane in hexane to give initially ethyl 4-methoxy-6-trifluoromethylindole-2-carboxylate (106 mg) then the **title compound** (240 mg, 24%), each as a white solid.

d) 4-Trifluoromethyl-6-methoxyindole-2-methanol Ethyl 4-trifluoromethyl-6-methoxyindole-2-carboxylate (220 mg, 0.76 mmol) in THF (5 ml) under argon was treated with a 1M solution of $LiAlH_4$ in THF (0.77ml) for 2h at 20°C. The reaction was quenched with water and ethyl acetate added. The organic phase was dried and evaporated to dryness to give the title compound as a white solid, (180 mg).

e) 4-Trifluoromethyl-6-methoxyindole-2-carboxaldehyde The alcohol from **d)** (160 mg, 0.65 mmol) in dichloromethane (20 ml) was stirred with manganese dioxide (555 mg, 10 eq.) at 20°C for 1 h. The solid was then filtered off and extracted with dioxan (200 ml). The combined filtrates were evaporated to give the title product as a cream coloured solid, (150 mg).

f) 2-[3-(4-Trifluoromethyl-6-methoxyindol-2-ylmethylamino)prop-1-ylamino]-1*H*-benzimidazole To **example 2a** (0.035 g, 0.18 mmol) was added the crude product from **e)** (0.040 g, 0.165 mmol) in methanol (3 ml), acetic acid (0.024 g) and sodium cyanoborohydride (0.016 g, 0.25 mmol). After 1.5 h the reaction mixture was applied to a 5 g SCX cartridge which was flushed with MeOH (20 ml). The cartridge was then eluted with 20 ml 0.2M NH_3 in MeOH,

and this eluate evaporated to dryness. Further purification by chromatography over silica gel eluting with an increasing concentration of 9:1 methanol/ammonia in dichloromethane gave the **title compound**, isolated as a colourless foam, (0.046 g, 67%); MS (ES^+) 418 (75%) MH^+, 191 (100%).

Example 13 - 2-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-5-methoxy-1*H*-benzimidazole

Example 1a (145 mg, 0.45 mmol) and 2-chloro-5-methoxybenzimidazole (36 mg, 0.2 mmol) were heated under argon to 100°C for 23 h. The crude product was purified by chromatography on silica gel eluting with 0-10% (9:1 methanol/.880 aq. ammonia) in dichloromethane to give the required product as a white foam, (30 mg, 32%); m/z (ES^+) 467/469/471 (19/38/20%) MH^+, 204 (100%).

Biological Data

1. Enzyme Inhibition – aminoacylation assay

Compounds of the present invention may be assayed for their ability to inhibit the enzyme methionyl tRNA synthetase (MRS), using recombinant *S. aureus* MRS, as follows:

Reaction Mix (per 1ml)

Stock	Volume (ul)	Final Concentration
100mM Tris/Cl, pH 7.9	600	30 mM
250 mM KCl		75 mM
125 mM ATP	40	2.5 mM
250 mM $MgCl_2$	80	10 mM
50 mM DTT	80	2 mM
0.5mM Met (S-35 hot and cold)	40	10 uM
Solid tRNA (Mixed E. coli MRE 600)	4mg/ml	2mg/ml
H_2O	160	

10 x Inhibitor (0 - 100 uM) 5 ul per well 0 - 10 uM

The reaction is started by adding 20 ul appropriately diluted pure enzyme (pre-incubated with inhibitor) to 25 ul reaction mix for 10 min at room temperature. The reaction is terminated by the addition of 100 ul 5% trichloroacetic acid, 10% glycerol. The TCA precipitate is harvested onto dry Unifilter GFC plates using a Packard Filtermate Cell Harvester. The filters are washed with 4 x 200ul of 50% industrial methylated spirit, before drying. 30 ul of Microscint 20 is added to each well and plates are counted on a TopCount. (Packard 96 well counter).

Reagents

Mixed E. coli MRE 600 tRNA and ATP were purchased from Boehringer-Mannheim, L-[^{35}S] methionine from Amersham and other reagents from Sigma.

Pure recombinant *S. aureus* MRS (EP application number 97300317.1, SmithKline Beecham) was obtained using standard purification procedures. The enzyme is diluted in Dilution Buffer which consists of 10 mM Tris / Cl, 2 mM DTT pH 7.9.

Results

Examples 1 to 13 have IC_{50} values against *S. aureus* MRS in the range <3 to 700 nM. All are highly selective with respect to the mammalian enzyme (no inhibition of rat MRS up to 1 uM).

2. Antibacterial Activity

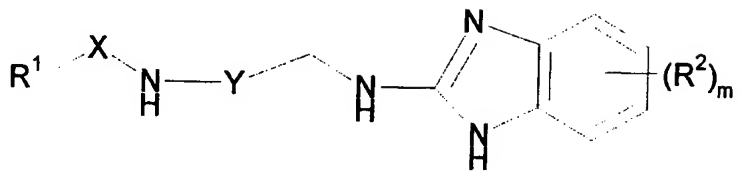
Compounds of the present invention were assayed for antibacterial activity against a range of pathogenic organisms (strains of *S aureus*, *S pneumoniae*, *E faecalis*, *H influenzae* and *M catarrhalis*) in a standard MIC assay modified by the inclusion of cyclodextrin, to assist with solubility.

Examples 1 - 12 had MIC's < 1μg/ml against some strains of the organisms *S. aureus*, *S. pneumoniae*, and *E. faecalis*; and MIC's against *M. Catarrhalis*, in the range 1 - 32 μg/ml.

Examples 1, 5, 8, 9 and 12 were active against *H. influenzae*.

Claims

1. A compound of formula (I):



(I)

in which:

R1 is an optionally substituted aryl or an optionally substituted heteroaryl ring;

R2 is selected from halo, cyano, hydroxy, (C1-6)alkyl (optionally substituted by halo, hydroxy, amino, mono to perfluoro(C1-3)alkyl, carboxy or (C1-6)alkoxycarbonyl), (C3-7)cycloalkyl, C(1-6)alkoxy, amino, mono- or di-(C1-6)alkylamino, acylamino, carboxy, (C1-6)alkoxycarbonyl, carboxy(C1-6)alkyloxy, (C1-6)alkylthio, (C1-6)alkylsulphinyl, (C1-6)alkylsulphonyl, sulphamoyl, mono- and di-(C1-6)alkylsulphamoyl, carbamoyl, mono- and di-(C1-6)alkylcarbamoyl, and heterocyclyl;

m is 0 or an integer from 1 to 3;

X is CH2 or CHR3 in which R3 is C(1-6)alkyl or is linked to the ortho position of an aryl or heteroaryl ring of R1 to form a 5 to 7 membered ring optionally including oxygen or nitrogen as a ring atom;

Y is C(1-3)alkylene or C(4-6)cycloalkylene;

including tautomeric forms of the imidazole ring; and

salts thereof, preferably pharmaceutically acceptable salts thereof; and excluding N-1H-benzimidazol-2-yl-N'-(phenylmethyl)-1,2-ethane diamine.

2. A compound of formula (I) as claimed in claim 1 in which R^1 when aryl is selected from phenyl and naphthyl, each of which may be optionally substituted with up to four substituents; or when heteroaryl is selected from pyrrolyl, thienyl, furanyl, pyridyl, quinolinyl, benzofuranyl, and indolyl, each of which may be optionally substituted with up to three substituents.

3. A compound of formula (I) as claimed in claim 1 or 2 in which aryl and heteroaryl groups for R^1 are phenyl and indolyl and thienyl, respectively.

4. A compound of formula (I) as claimed any one of claims 1 to 3 in which X is CH_2 or forms with R^2 a 5-7-membered ring fused to an aryl ring or a heteroaryl ring which includes oxygen or nitrogen as a ring atom.

5. A compound of formula (I) as claimed any one of claims 1 to 4 in which R^1X is benzyl, chroman-4-yl, 1,2,3,4-tetrahydroquinolin-4-yl, indol-2-ylmethyl, and thien-2-ylmethyl in which the aryl/heteroaryl ring may be optionally substituted.

6. A compound of formula (I) as claimed any one of claims 1 to 5 in which Y is a C_2 alkylene chain.

7. A compound of formula (I) as claimed in claim 1 selected from any one of the compounds named in the main title of Examples 1 to 13.

8. A compound of formula (I) as claimed in claim 7 selected from:

2-[3-(6,8-Dibromo-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]-1*H*-benzimidazole;
2-[3-(4,6-Dichloroindol-2-ylmethylamino)prop-1-ylamino]-1*H*-benzimidazole;
2-[3-(6-Ethyl-8-iodo-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]-1*H*-benzimidazole;
2-{3-[4,6-Dichloro-1-(2-hydroxyethyl)-1*H*-indol-2-ylmethylamino]prop-1-ylamino}-1*H*-benzimidazole;
2-[3-(2-Ethoxy-5-iodo-3-methylbenzylamino)prop-1-ylamino]-1*H*-benzimidazole; and
2-[3-(4-Trifluoromethyl-6-methoxyindol-2-ylmethylamino)prop-1-ylamino]-1*H*-benzimidazole.

9. A pharmaceutical composition comprising an antibacterially effective amount of a substance or compound of formula (I) as claimed in claim 1 together with a pharmaceutically acceptable carrier or excipient.

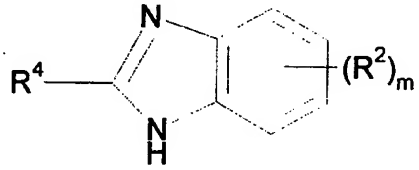
10. A compound of formula (I) as claimed in for use in therapy.

11. A compound of formula (I) as claimed in for use in the treatment of bacterial infections.

12 Use of a compound of formula (I) as claimed in claim 1 in the manufacture of a medicament for use in the treatment of bacterial infections.

13. A process for preparing a compound of formula (I) as claimed in claim 1 which process comprises

(i) reacting an imidazole compound of formula (II):



(II)

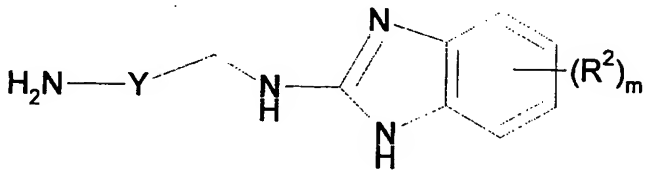
in which R^2 and m are as defined in claim; and
R^4 is a leaving group such as halo, for instance chloro or $C_{(1-6)}$ alkylthio;
with an amine of the formula (III):

$$R^1XNHYCH_2NH_2$$

(III)

in which R^1, X and Y are as defined in claim 1;
or an activated derivative thereof;
under nucleophilic displacement conditions; or

(ii) reacting a compound of formula (IV):



(IV)

in which m, R^2 and Y are as hereinbefore defined;
with either:

(a) for a compound of formula (I) in which X is CH_2, an aldehyde of formula (V):

$$R^1CHO \qquad (V)$$

in which R^1 is as hereinbefore defined;
under reductive alkylation conditions;

(b) for a compound of formula (I) in which X is CH_2 substituted by $C_{(1-6)}$ alkyl or in which R^1 and X are linked by a 5-7-membered ring opt.cont. oxygen or nitrogen,, a ketone of formula (VI):

$$R^1R^3CO \qquad (VI)$$

in which R^1 and R^3 are as hereinbefore defined;
under reductive alkylation conditions.

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/EP 00/04435

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D235/30 C07D401/12 C07D403/12 C07D405/12 C07D409/12
A61K31/4184 A61K31/4709 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LEE J ET AL: "Methionyl Adenylate Analogues as Inhibitors of Methionyl-tRNA Synthetase" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 9, no. 10, 17 May 1999 (1999-05-17), pages 1365-1370, XP004164893 ISSN: 0960-894X the whole document	1,9-12
A	LEE J ET AL: "Methionine Analogues as Inhibitors of Methionyl-tRNA Synthetase" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 8, no. 24, 15 December 1998 (1998-12-15), pages 3511-3514, XP004150358 ISSN: 0960-894X the whole document	1,9-12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 September 2000	21/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Allard, M

Form PCT/ISA/210 (second sheet) (July 1992)

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 00/04435

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 99 55677 A (SMITHKLINE BEECHAM PLC) 4 November 1999 (1999-11-04) the whole document	1,9-12
P,A	WO 00 21949 A (SMITHKLINE BEECHAM PLC) 20 April 2000 (2000-04-20) the whole document	1,9-12

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr nal Application No
PCT/EP 00/04435

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9955677 A	04-11-1999	AU 3523599 A	16-11-1999
WO 0021949 A	20-04-2000	AU 6339499 A	01-05-2000